REMARKS

Reconsideration of the rejections set forth in the Office Action mailed January 12, 2005, is respectfully requested. Claims 1 and 33 have been amended. Claims 46-63 have been newly added. These claims correspond to original claims 2-3, 24-32, 38, and 40-45, which were canceled in the preliminary amendment filed on April 16, 2004. Claims 1, 4-23, 33-37, 39, and 46-63 remain pending in this case. Specification support for these amendments can be found at, e.g., paragraphs 0012, 0013, 0018-19, 0020, 0023, 0047-48, 0054-79, 0098, 0113, 0118, 0133 and Table 9, 0134, and 0145. Therefore, these amendments are made without introducing new matter.

Amendments to the Specification

Applicants discovered a typographical error in the chemical structure of dalbavancin on page 11 -- the connectivity of one of the bonds to a phenyl ring is misplaced. The correct structure of dalbavancin is well known and is set forth elsewhere in the present application. As published in U.S. Patent No. 5,750,509 (Attached as Exhibit A, see formula (I) in Col. 1), incorporated by reference in the present application at paragraphs 0039 and 0255, the connectivity to the phenyl ring at position (15) of the carbon is *para* to the OH substituent, not *meta*. Therefore, applicants respectfully request correction of this structure.

Double Patenting

Claims 1-45 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 57-78 of co-pending Application Serial No. 10/714,261, claims 1-25 of co-pending Application Serial No.

10/839,379, and claims 12-24, 28-32, 37-43, and 54-66 of co-pending Application Serial No. 10/828,439.

With respect to the rejection over co-pending Application Serial No. 10/714,261, this application has since issued as U.S. Patent No. 6,900,175. Without conceding the propriety of the rejection, applicants file a terminal disclaimer over U.S. Patent No. 6,900,175 herewith.

With respect to the other rejections, these are provisional rejections as none of the pending applications have yet issued. Therefore, Applicants will address these rejections once the applications are allowed or have issued as the pending claims may change during prosecution.

Art Rejections

Claims 1-4 and 33-45 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by "Dalbavancin Tested for Soft Tissue Infections " (2001). Claims 1-45 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over "Dalbavancin Tested for Soft Tissue Infections " (2001). The examiner has taken the position that although the cited references do not disclose administration of at least two doses separated by at least five to ten days, it would have been within routine experimentation by a person having ordinary skill in the art to determine optimal dosage intervals.

Claims 1 and 33 have each been amended to include the step of "*administering initial and subsequent therapeutically effective doses of dalbavancin in a pharmaceutically acceptable carrier to the patient, wherein each dose is separated by five to ten days.*" Additionally, claim 1 specifies that "*the amount of the initial dose is about 1.5 to about 3 times the amount of dalbavancin contained in the subsequent dose.*" Claim 33 has been amended to specify that "*the*

amount the initial dose is about 500 mg to about 5000 mg, and wherein the amount of the initial dose is about 1.5 to about 3 times the amount of dalbavancin contained in the subsequent dose."

The examiner has taken the position that, although the cited reference does not disclose the dosage regimen encompassed by the claims as filed for the treatment of soft tissue infections, it would have been within routine experimentation to determine an optimal dosage regimen for dalbavancin. Applicants respectfully disagree with the examiner's position and assert that it would not have been within routine experimentation to determine an optimal dosage regimen for dalbavancin.

Applicants respectfully assert that the conventional wisdom for several groups of widely used antibiotics, including penicillins, cephalosporins, carbapenems, and glycopeptide antibiotics (a class to which dalbavancin belongs), is that the time during which the serum concentrations exceed the minimum inhibitory concentration (MIC) of the pathogen (T > MIC) is the best predictor of efficacy. This general principle is well known for β-lactams,[1] vancomycin,[2] and

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[1] See, e.g., BURGESS, D.S. et al. "*Pharmacokinetics and Pharmacodynamics of Piperacillin/Tazobactam When Administered by Continuous Infusion and Intermittent Dosing.*" CLIN THER. 2002 Jul. 24(7):1090-1104 ("Although intermittent bolus dosing is currently the standard of practice for many antimicrobial agents, beta-lactams exhibit time-dependent bacterial killing. Maximizing the time above the minimum inhibitory concentration (MIC) for a pathogen is the best pharmacodynamic predictor of efficacy. Use of a continuous infusion has been advocated for maximizing the time above the MIC compared with intermittent bolus dosing." (Abstract) (Attached as Exhibit B)

[2] MacGowan, A.P. "Pharmacodynamics, Pharmacokinetics, and Therapeutic Drug Monitoring of Glycopeptides" THEREAPEUTIC DRUG MONITORING 20: 473-477 (1998) ("The pharmacodynamics of glycopeptides studied in several animal models support the concept that high initial concentrations offer no advantage in bacterial killing or mortality, whereas higher, sustained concentrations or more frequent dosing have improved survival in animal models of infective endocarditis.") (P. 473) (Attached as Exhibit C)

ROSS, Gigi H. et al. "Glycopeptide Pharmacodynamics" in ANTIMICROBIAL PHARMACODYNAMICS IN THEORY AND CLINICAL PRACTICE. 177-204 (2002) ("On the basis of

teicoplanin.[3] Therefore, the prior art teaches that smaller, frequent doses are preferred over larger, infrequent doses in order to maintain serum concentrations above the MIC, while at the same time avoiding toxicity. In fact, under this principle, optimization is achieved by keeping serum concentration just above MIC by frequent administration, e.g., intravenous administration. By maintaining the lowest possible level that is just above MIC, toxicity is believed to be minimized.

Contrary to this conventional wisdom, applicants have unexpectedly discovered a dramatic increase in efficacy by administering doses of dalbavancin at intervals of about 5-10 days, or alternatively, at approximately a week. Tables 4 and 5, on pages 33 and 35 of the specification, respectively, show the results of such a regimen. As seen in Table 4, the clinical success rate ("clinically evaluable at FU") shows a dramatic increase in efficacy for the two-dose regimen (94.1 %) compared to the single dose regimen (61.5 %), even though both maintain serum concentration above MIC for the intended course of treatment. Similarly, in Table 5, the two-dose regimen had a success rate of 87.5 % against the total organisms tested, as compared to a rate of 43.8 % for the single dose regimen, even though both maintain serum concentration above MIC for the intended course of treatment. This dramatic improvement in efficacy was

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limited in vitro studies, T > MIC appears to most closely predict efficacy of vancomycin. Therefore, the length of time the antibiotic concentration exceeds the MIC of the offending organism and not the height of the peak above the MIC, as in aminoglycosides, should be considered the goal of the dosing of vancomycin.") (P. 184) (Attached as Exhibit D)

[3] HARDING, I. et al., "*Teicoplanin Therapy for Staphylococcus aureus septicaemia: relationship between pre-dose serum concentrations and outcome.*" J. ANTIMICROBIAL CHEMOTHERAPY 45: 835-841 (2000) ("These data would indicate that transient high peak serum concentrations of teicoplanin are not likely to be of benefit in killing bacteria or curing infection and that sustained concentrations over the MIC will be of benefit in terms of improving extravascular drug penetration and cure rates.") (P. 839) (Attached as Exhibit E)

completely unexpected and contrary to the teaching of the prior art, which suggested a daily dosing regimen for dalbavancin. (See, e.g., "Molecule of the Month (Nov. 2000) "Serum bactericidal activity was evident within 24 hours of administration of a 360-mg dose, indicating the feasibility of once-daily dosing." (Attached as Exhibit F)) The prior art for dalbavancin and for other glycopeptide antibiotics therefore teaches away from the claimed invention.

Claims 1 and 33 are therefore patentably distinct from the cited art. (*See In Re Soni*, 54 F.3d 746, 751, 34 U.S.P.Q.2d 1684, 1688 (Fed. Cir. 1995) "when an applicant demonstrates substantially improved results, ... and states that the results were unexpected, this should suffice to establish unexpected results in the absence of evidence to the contrary.") Claims 4-23 and 46-56 are dependent on claim 1, and are therefore patentably distinct from the cited art for the same reasons applicable to claim 1. Claims 34-37, 39, 57-63 are dependent on claim 33, and are therefore patentably distinct from the cited art for the same reasons applicable to claim 33. The rejections based on prior art should therefore be withdrawn.

CONCLUSION

For all the foregoing reasons, applicants assert that the claims are in condition for allowance. Favorable action on the merits of the claims is therefore earnestly solicited. If any issues remain, please contact the applicants' undersigned representative at (949) 737-2900. The Commissioner is hereby authorized to charge any fees that may be required in connection with the filing of these documents to Deposit Account No. 50-2862.

Respectfully submitted,

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